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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/523,271	09/06/2005	Andrew Simon Goldsborough	CGS-102	5614

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EXAMINER	
POHNERT, STEVEN C	

ART UNIT	PAPER NUMBER
1634	

MAIL DATE	DELIVERY MODE
09/25/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/523,271	GOLDSBOROUGH, ANDREW SIMON	
	Examiner	Art Unit	
	STEVEN C. POHNERT	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25 and 45-65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-25 and 45-65* is/are rejected.

7)☒ Claim(s) *46-65* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/24/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to papers filed 6/24/2008.

The response has amended claims 1, 10, and 22.

The response has further added new claims 45-65.

Claims 1-25 and 45-65 are pending.

The objection to claims 15 and 22 have been withdrawn in view of the amendment.

Claims 1-25 and 45-65 are being examined.

Claim Objections

1. Claims 46-65 are objected to because of the following informalities: Claim 46 recite "a biological sample, " "said biological sample," and "the sample" interchangeably. The interchangeable use of these terms presents an awkward claim. It is suggested that applicant use consistent language throughout the claim, to improve the clarity of the claim. Appropriate correction is required.

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1-12, 13, 15, 16, 22-25 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goldsborough (WO00/75302 , published December 14, 2000) in view of Greene et al (Protective groups in organic synthesis, Third edition (1999) pages 160-161).

This rejection has been maintained, but modified to improve clarity, reflect amendment to the claims and reject claim 45.

With regards to claim 1, Goldsborough et al teaches a method of treating a sample so that the 2'-OH of RNA is modified and isolating the nucleic acid following modification (see page 3, 1st paragraph). Goldsborough teaches the method provides for obtaining intact full-length copies of RNA isolated from cellular sources or extracellular fluids. Goldsborough teaches obtaining a biological sample (page 4, 2nd full paragraph). Goldsborough teaches, "the RNA can be deprotected by cleavage of the modifying group with 50% ammonia treatment, 10-40mM KCN (final concentration) in 95% EtOH, K2C03 in aqueous methanol or other conditions which are known to lead to the cleavage of the ester linkage (see Protective Groups In Organic Chemistry, 2nd edition, Ed. T. W. Greene, Wiley- Interscience)" (see page 41, 1st paragraph). Goldsborough teaches the RNA is then collected and purified further if required (see page 41, 1st paragraph). Goldsborough thus teaches a method of collecting a biological sample, treating the sample to protect the 2'OH, isolating the treated sample, and deprotecting.

With regards to claim 2, Goldsborough teaches the RNA is isolated from virus, bacteria (cells), blood or body fluids (see page 4, 2nd and 3rd paragraphs and page 24, last full paragraph).

With regards to claim 3, Goldborough teaches, "RNA can be derived from a biological material such as bacteria, viruses such as those causing infection in humans, animals or plants, viroids, or cells such as fungal, animal and plant cells." Goldsborough thus teaches the biological fluid comprises a pathogen.

With regards to claims 4 and 5, Goldborough teach the nucleic acid is single stranded RNA and the 2'-OH is modified (see abstract).

With regards to claim 6, Goldsborough teaches an organic solvent is used in the reaction medium (see page 13). Goldsborough thus teaches the step (b) takes place in an organic solvent.

With regards to claim 7, Goldsborough teaches the use of dimethyl sulphoxide (see page 13), which has a flash point above 37°C.

The specification set forth no limiting definition of homogeneous.

With regards to claim 8, Goldsborough teaches the use of DMSO. DMSO is capable of forming a homogenous solution with human blood when mixed at a 5:1 ratio.

With regards to claim 10, Goldsborough teaches attaching to BCPB beads and then washing the beads with ethanol and water (see page 47). Goldsborough teaches the RNA is released from the first solid (see page 47, last 3 lines). Goldsborough thus teaches a method of binding a nucleic acid to a solid phase, washing the solid phase to remove contaminants, and eluting for the solid phase.

With regards to claim 11, Goldsborough teaches the use of magnetic or paramagnetic particles with a polymeric linear, globular or cross-linked molecule(see page 23, first full paragraph).

With regards to claim 12, Goldsborough teaches his method allows modification of the phosphate group to the beads or particles of the invention. Thus Goldsborough teaches the solid phase contains a metal or metal ion capable of coordinating with phosphate. Goldsborough teaches use of silicon beads.

With regards to claim 13 and 15, Goldsborough teaches the release of RNA using ammonia (see page 41, line 12).

With regards to claim 16, Goldsborough teaches the use of Centricon-50 columns to separate the salts (see page 43, 1st full paragraph). Goldsborough thus teaches removing chelator by filtration.

With respect to 22, the courts have held that selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results (In re Burhans, 154 F.2d 690, 69 USPQ 330 (CCPA 1946). See MPEP 2144.04 IV.C.

With regards to claim 22, Goldsborough teaches the RNA can be deprotected, then collected and purified by for example oligo (dT) selection of mRNA (page 41). Goldsborough thus teaches binding the RNA to a solid phase, deprotecting, washing and eluting the nucleic acids from the solid phase.

With regards to claim 23, Goldsborough teaches the use of silica beads (see page 36).

With regards to claim 24, Goldsborough teach binding of BMV RNA to BCPB beads and subsequent hybridization of a radio labeled BMV RNA probe to the BMV-RNA-bead complex (see page 48). Thus Goldsborough teaches isolation of the radio labeled BMV-RNA by the complementary BMV-RNA-bead complex.

With regards to claim 25, Goldsborough teaches Binding of 512 ng of BV RNA to BCPB beads, subsequent reaction with a second modifier, such as biotin, release (deprotection) of the RNA from the beads before, attachment to streptavidin beads by the biotin (see page 47). Thus Goldsborough teaches the RNA is isolated and subject to a deprotecting step (release from BCPB beads) before attachment to a solid phase (streptaviding beads).

With regards to claim 45, Goldsborough teaches RT PCR of the isolated nucleic acid (example 15, page 57).

Goldsborough does not teach a method of stabilizing and isolating a nucleic acid from a sample, wherein the nucleic acid is deprotected by treatment with a primary amine.

However, Greene et al teaches the cleavage of ester linkages by use of $HSCH_2CH_2NH_2$ or $H_2NCH_2CH_2NH_2$ (ethylenediamine) (see page 161, #1) (claim 9).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the primary amine or ethylenediamine ester cleavage method of Greene et al as a reactant to remove the protecting group in the method of Goldsborough. The artisan would be motivated to use ethylenediamine because it is specifically taught by Greene. The ordinary artisan would be motivated

because Goldsborough suggests the use of any ester cleavage reagent and specifically directs the artisan to the work of Greene. The artisan would thus be substituting one know method of ester cleavage reagent with another know method of ester cleavage and thus would have a probability of success.

Response to Arguments

The response traverses the rejection based on Gouldsorough and Greene by presenting a quotation from the instant specification, ""Whilst many chemical deprotecting methods are also known for removing acetyl groups (Protecting Groups in Organic Synthesis, Greene and Wuts, 2nd Edition, Wiley Interscience) most if not all involve either a base or acid conditions that are likely to lead to extensive cleavage of the desired RNA during deprotection." It is noted the teachings that are quoted are from the instant specification and are not from the office action or references used in the instant rejection. These arguments have been thoroughly reviewed but are not considered persuasive as the claims are not limited to RNA, but any nucleic acid. Further on page 41 of Gouldsborough, Gouldsborough teaches deprotection , "or other conditions which are known to lead to the cleavage of the ester linkage (see Protective Groups In Organic Chemistry, 2nd edition, Ed. T. W. Greene, Wiley Interscience)." Thus the prior art of Goldsborough contrary to the assertion of the response specifically directs the artisan to the teachings of Greene et al.

The response further asserts the instant application would not have directed one of skill in the art to Greene as the expected results of Greene would have been degraded end products. These arguments have been thoroughly reviewed, but are not

considered persuasive as the instant application are not being used in the 103. Thus arguments directed to the assertion of teaching away from Greene et al in the instant specification are moot as they are not part of the instant rejection. Further the arguments to the degradation or undegraded nucleic acids being isolated are not limitations that are present in the claims. Further the response has provided no evidence the nucleic acids would indeed be degraded. First, MPEP 716.01(c) makes clear that "The arguments of counsel cannot take the place of evidence in the record. In re Schulze , 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long - felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant." Here, the statements regarding the degradation of nucleic acids have not been supported by evidence.

This should not be construed as an invitation for providing evidence. As further stated in the MPEP 716.01 regarding the timely submission of evidence:

A) Timeliness.

Evidence traversing rejections must be timely or seasonably filed to be entered and entitled to consideration. In re Rothermel, 276 F.2d 393, 125 USPQ 328 (CCPA 1960). Affidavits and declarations submitted under 37 CFR 1.132 and other evidence traversing rejections are considered timely if submitted:

(1) prior to a final rejection,

(2) before appeal in an application not having a final rejection, or

(3) after final rejection and submitted

(i) with a first reply after final rejection for the purpose of overcoming a new ground of rejection or requirement made in the final rejection, or

(ii) with a satisfactory showing under 37 CFR 1.116(b) or 37 CFR 1.195, or

(iii) under 37 CFR 1.129(a).

Further applicant has provided an article by Perreault and Anslyn teaching primary amines are recognized in the art to cleave nucleic acids. The teachings by Perreault are drawn to RNA cleavage by tranesterification. The examiner appreciates the presentation of Perreault and the teaching with respect to RNA cleavage, however as noted previously the claims do not require the RNA, or nucleic acid be 100% intact. Further the assertion primary amines can cleave RNA does not prove or suggest the inoperability of the instant 103, but merely suggests unprotected RNA can be cleaved and/or degraded by the primary amines. The examiner supports the art of record by providing the teachings of Hogrefe et al (Nucleic acids Research (1993) volume 21, pages 2031-2038), which teaches that ethylenedianamine allows for deprotection of nucleic acids with little backbone digestion (figure 1). Thus Hogrefe et al demonstrates that one of skill in the art would not expect to get only degrade nucleic acids.

Finally, the specification contradicts the assertion that there is extensive degradation of RNA by use of primary amines by teaching, "We have unexpectedly demonstrated that primary amines can not only remove protecting groups from the 2'-

OH position of RNA but also lead to only limited cleavage of the phosphodiester backbone of RNA as would be expected for a base" (page 8, 1st paragraph). Thus the specification contradicts the assertion of the response that use of primary amines cleaves all RNA.

Thus the combination of Gouldsborough and Greene is maintained as the response has provided only arguments of counsel as to the asserted degradation of RNA by the combination, but has not provided any evidence. Further, the arguments directed to the cleavage or degradation do not reflect the full scope of the claimed invention and thus provide not arguments to DNA. Finally, the specification and Hogrefe teach the combination worked even in RNA to which most of the arguments of the response are dressed.

The response concludes by asserting that comparative data in the specification must be considered in reaching the conclusion of obvious and cites *In re Margolis*. These arguments have been thoroughly reviewed but are not considered persuasive as the cite portion of page 12 merely indicate there is a decreased protein binding in the instant method compared to previous methods, this decreased protein binding is not a limitation of the claims, thus arguments to such are moot.

4. Claim 14 rejected under 35 U.S.C. 103(a) as being unpatentable over Goldsborough (WO00/75302 , published December 14, 2000) in view of Greene et al (Protective groups in organic synthesis, Third edition (1999) pages 160-161) as applied to claims 1-13, 15, 16 and 22-25 above, and further in view of Padhye (US Patent 5,808,041, issued September 15, 1998).

This rejection has been maintained, but modified to improve clarity.

The teachings of Goldsborough and Greene are set forth above.

Goldsborough and Green do not teach the elution of nucleic acid using EGTA with a pH above 9.

However, Padhye et al teaches elution in sample containing EDTA or EGTA (see column 6, lines 26-29). Padhye further teaches elution in of nucleic acids in buffers with a pH about 8.5 (see column 9, lines 22-24). A pH of about 8.5 is about 9.

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the EGTA solution of pH 9 in the method of Goldsborough using silica beads to release the modified RNA. The skilled artisan would be motivated to substitute the method of elution taught by Goldsborough with the EGTA solution of Padhye, because Padhye demonstrates that EGTA solutions are known in the art to elute nucleic acids from silica beads. The artisan would have reasonable expectation of success as the artisan is merely substituting one elution reagent for another and both are art accepted methods.

Response to arguments

The response asserts that the arguments to the combination of Goldsborough and Greene are not remedied by Padhye. These arguments have been thoroughly reviewed but are not considered persuasive as the response has asserted the combination of Goldsborough and Greene would result in degraded RNA, however the claims are drawn to nucleic acids. Further, MPEP 716.01(c) makes clear that "The arguments of counsel cannot take the place of evidence in the record. In re Schulze ,

346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long - felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant." Here, the statements regarding the degraded RNA have not been supported by evidence. It is noted that this argument by applicant suggests inoperability of its own invention as the response does not appear to suggest how the use of the primary amine in the instant invention allows for intact RNA.

This should not be construed as an invitation for providing evidence. As further stated in the MPEP 716.01 regarding the timely submission of evidence:

A) Timeliness.

Evidence traversing rejections must be timely or seasonably filed to be entered and entitled to consideration. In re Rothermel, 276 F.2d 393, 125 USPQ 328 (CCPA 1960). Affidavits and declarations submitted under 37 CFR 1.132 and other evidence traversing rejections are considered timely if submitted:

(1) prior to a final rejection,

(2) before appeal in an application not having a final rejection, or

(3) after final rejection and submitted

(i) with a first reply after final rejection for the purpose of overcoming a new ground of rejection or requirement made in the final rejection, or

(ii) with a satisfactory showing under 37 CFR 1.116(b) or 37

CFR 1.195, or

(iii) under 37 CFR 1.129(a).

5. Claims 17-21 and 46-56, 58-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goldsborough (WO00/75302 , published December 14, 2000) in view of Greene et al (Protective groups in organic synthesis, Third edition (1999) pages 160-161) as applied to claim 1-13, 15, 16 and 22-25 above, and further in view of Michelsen et al (US Patent 6,355,792, Issue March 12, 2002).

With regards to claim 46, Goldsborough et al teaches a method of treating a sample so that the 2'-OH of RNA is modified and isolating the nucleic acid following modification (see page 3, 1st paragraph). Goldsborough teaches the method provides for obtaining intact full-length copies of RNA isolated from cellular sources or extracellular fluids. Goldsborough teaches obtaining a biological sample (page 4, 2nd full paragraph). Goldsborough teaches, "the RNA can be deprotected by cleavage of the modifying group with 50% ammonia treatment, 10-40mM KCN (final concentration) in 95% EtOH, K2C03 in aqueous methanol or other conditions which are known to lead to the cleavage of the ester linkage (see Protective Groups In Organic Chemistry, 2nd edition, Ed. T. W. Greene, Wiley- Interscience)" (see page 41, 1st paragraph). Goldsborough teaches the RNA is then collected and purified further if required (see page 41, 1st paragraph). Goldsborough thus teaches a method of collecting a biological sample, treating the sample to protect the 2'OH, isolating the treated sample, and deprotecting.

With regards to claims 47 and 48, Goldsborough teaches the RNA is isolated from virus, bacteria (cells), blood or body fluids (see page 4, 2nd and 3rd paragraphs and page 24, last full paragraph).

With regards to claims 49 and 50, Goldborough teach the nucleic acid is single stranded RNA and the 2'-OH is modified (see abstract).

With regards to claim 51, Goldsborough teaches the use of dimethyl sulphoxide (see page 13), which has a flash point above 37°C.

The specification set forth no limiting definition of homogeneous.

With regards to claim 52, Goldsborough teaches the use of DMSO. DMSO is capable of forming a homogenous solution with human blood when mixed at a 5:1 ratio.

With regards to claim 54, Goldsborough teaches the use of magnetic or paramagnetic particles with a polymeric linear, globular or cross-linked molecule(see page 23, first full paragraph).

With regards to claim 55, Goldsborough teaches his method allows modification of the phosphate group to the beads or particles of the invention. Thus Goldsborough teaches the solid phase contains a metal or metal ion capable of coordinating with phosphate. Goldsborough teaches use of silicon beads.

With regards to claim 56, Goldsborough teaches the release of RNA using ammonia (see page 41, line 12).

With regards to claim 58, Goldsborough teaches the use of Centricon-50 columns to separate the salts (see page 43, 1st full paragraph). Goldsborough thus teaches removing chelator by filtration.

With regards to claim 59, Goldsborough teach binding of BMV RNA to BCPB beads and subsequent hybridization of a radio labeled BMV RNA probe to the BMV-RNA-bead complex (see page 48). Thus Goldsborough teaches isolation of the radio labeled BMV-RNA by the complementary BMV-RNA-bead complex.

Goldsborough does not teach a method of stabilizing and isolating a nucleic acid from a sample, wherein the nucleic acid is deprotected by treatment with a primary amine.

However, Greene et al teaches the cleavage of ester linkages by use of $HSCH_2CH_2NH_2$ or $H_2NCH_2CH_2NH_2$ (ethylenediamine) (see page 161, #1) (claim 9).

The courts have stated:

similar properties may normally be presumed when compounds are very close in structure. Dillon, 919 F.2d at 693, 696, 16 USPQ2d at 1901, 1904. See also In re Grabiak, 769 F.2d 729, 731, 226 USPQ 870, 871 (Fed. Cir. 1985) ("When chemical compounds have very close' structural similarities and similar utilities, without more a prima facie case may be made."). Thus, evidence of similar properties or evidence of any useful properties disclosed in the prior art that would be expected to be shared by the claimed invention weighs in favor of a conclusion that the claimed invention would have been obvious. Dillon, 919 F.2d at 697-98, 16 USPQ2d at 1905; In re Wilder, 563 F.2d 457, 461, 195 USPQ 426, 430 (CCPA 1977); In re Linter, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972) (see MPEP 2144.08(d)).

Therefore the substitution of diethylenetriamine, triethylenetetramine, lysine, or arginine for the ethylenediamaine of Greene would have been an obvious variation over the prior art.

However, Greene et al teaches the cleavage of ester linkages by use of $HSCH_2CH_2NH_2$ or $H_2NCH_2CH_2NH_2$ (ethylenediamine) (see page 161, #1) (claim 9).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the primary amine or ethylenediamine ester cleavage method of Greene et al as a reactant to remove the protecting group in the method of Goldsborough. The artisan would be motivated to use ethylenediamine because it is specifically taught by Greene. The ordinary artisan would be motivated because Goldsborough suggests the use of any ester cleavage reagent and specifically directs the artisan to the work of Greene. The artisan would thus be substituting one know method of ester cleavage reagent with another know method of ester cleavage and thus would have a probability of success.

Goldsborough et al and Greene do not teach the use of hydroxapatite as a solid phase (claim 17 and 46-56, 58-65), wherein the hydroxyapatite is prewashed with a phosphate containing compound (claim 18), washing with a primary amine (claims 19 and 20), or wherein deprotection comprises step (ii) (claim 21).

However, Michelsen teaches a method of isolating nucleic acids by their binding to silica gel or hydroxypatite (see abstract and column 2, lines 35-36). MIchelsen teaches the use of "appropriate magnetic beads" (column 3, lines 5-10). Michelsen teaches washing the resins bound with the nucleic acids with Tris-HCl (see column 4,

line 42). Michelsen teaches eluting with a Tris contatining buffer (see column 4, line 42). Tris is an amine and a primary amine. Michelsen further teaches the hydoxypatite is treated with DNA/RNA mixture before washing. RNA and DNA are phosphate containing compounds. Thus Michelsen teaches pretreatment of hydroxypatite with a phosphate containing compounds.

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute the hydroxypatite of Michelsen for the silica beads of Goldsborough and Greene with a reasonable expectation of success. The ordinary artisan would have substitute hydroxpatite for the silica of Goldsboroughand Greene because Michelsen teaches the use of either silica gel or hydroxypatite for binding of nucleic acid were known and accepted methods of nucleic acid isolation at the time of the invention. Thus the substitution of hydroxypatite for silica beads would merely be a substitution of one art accepted nucleic acid binding agent for another DNA binding agent. The artisan would have a high probability of success as the substitution is an art accepted alternative.

Response to arguments'

The response asserts that the arguments to the combination of Goldsborough and Greene are not remedied by Michelsen. These arguments have been thoroughly reviewed but are not considered persuasive as the response has asserted the combination of Goldsborough and Greene would result in degraded RNA, however the claims are drawn to nucleic acids. Further, MPEP 716.01(c) makes clear that "The arguments of counsel cannot take the place of evidence in the record. In re Schulze ,

346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long - felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant." Here, the statements regarding the degraded RNA have not been supported by evidence. It is noted that this argument by applicant suggests inoperability of its own invention as the response does not appear to suggest how the use of the primary amine in the instant invention allows for intact RNA.

This should not be construed as an invitation for providing evidence. As further stated in the MPEP 716.01 regarding the timely submission of evidence:

A) Timeliness.

Evidence traversing rejections must be timely or seasonably filed to be entered and entitled to consideration. In re Rothermel, 276 F.2d 393, 125 USPQ 328 (CCPA 1960). Affidavits and declarations submitted under 37 CFR 1.132 and other evidence traversing rejections are considered timely if submitted:

(1) prior to a final rejection,

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(3) after final rejection and submitted

(i) with a first reply after final rejection for the purpose of overcoming a new ground of rejection or requirement made in the final rejection, or

(ii) with a satisfactory showing under 37 CFR 1.116(b) or 37

CFR 1.195, or

(iii) under 37 CFR 1.129(a).

6. Claim 57 is rejected under 35 U.S.C. 103(a) as being unpatentable over Goldsborough (WO00/75302 , published December 14, 2000), Greene et al (Protective groups in organic synthesis, Third edition (1999) pages 160-161) , and Michelsen et al (US Patent 6,355,792, Issue March 12, 2002) as applied to claim17-21 and 46-56, 58-65 above, and further in view of Padhye (US Patent 5,808,041, issued September 15, 1998).

The teachings of Goldsborough, Greene and Michelsen are set forth above. Michelsen additional teaches the use of EDTA at pH 9.0 to elute the nucleic acids (column 3, line 60 to column 4, line 5).

Goldsborough, Greene and Michelsen do not teach the use of EGTA as the chelator and elution above a pH of 9.0.

However, Padhye et al teaches elution in sample containing EDTA or EGTA (see column 6, lines 26-29). Padhye further teaches elution in of nucleic acids in buffers with a pH about 8.5 (see column 9, lines 22-24). A pH of about 8.5 is about 9.

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the EGTA solution of pH 9 in the method of Goldsborough, Greene and Michelsen using hydroxypatite beads to release the modified RNA. The skilled artisan would be motivated to substitute the method of elution taught by Goldsborough, Greene and Michelsen with the EGTA solution of

Padhye, because Padhye demonstrates that EGTA solutions are known in the art to elute nucleic acids from beads.

Summary

No claims are allowed over prior art cited.

Conclusion

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEVEN C. POHNERT whose telephone number is (571)272-3803. The examiner can normally be reached on Monday-Friday 6:30-4:00, every second Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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